KTR

Final Report

TBR-0008-14

Silver Ion Sterilizer

Single oral-administered toxicity test of silver ion sterilizer on rats

President of Korea Testing & Research Institute

Study Overview

Study Title: Single oral-administered toxicity test of silver ion sterilizer on rats

Study Number: TBR-0008-14

Sponsor:

Name: CNL Co. Ltd.

Location: 1 Yeonseoidaegil, Heungeupmyeon, Wonju City, Gangwon-do (#304 Business Start-up and Childcare Center for the Disabled)

CEO: KIM, Kyeong Su

Contact: Tel. 033-764-2116 Fax. 033-764-2117

Test Facility:

Name: Health Care Research Laboratory of the Korea Testing & Research Institute (KTR)

Location: 12-63 Sandan-gil, Hwasun-eup, Hwasun-gun, Jeollanam-do

Operator in charge: PARK, Jong Il

Contact: Tel. 061-370-7810 Fax. 061-370-7777

Test Method:

-Ministry of Food & Drug Safety Announcement no. 2014-136 (July, 30, 2014), "Toxicity Test Standards for Drugs etc.", [Attachment 1] Single Administered Toxicity Test

LEE, Taek Jin, B. S. Date

Study Director

Health Care Research Laboratory, KTR

This is a report for the test substance provided by the sponsor.

Study Staffs

The following study staffs conducted the important testing steps of the study and reported the results thereof according to the standard operating guidelines of the Health Care Research Laboratory, KTR.

Staff in charge of the study: KIM, Jun Ho/B.S.

KIM, Sang Ho/B.S.

Paek, Hyeong Seon/D.V.M., M.S.

Staff in charge of preparing the test substances:

LEE, Taek Jin/B.S.

Staff in charge of animal management:

KIM Yong Woo/B.S.

Staff in charge of quarantine: LEE, Taek Jin/B.S.

Staff in charge of statistical processing of data:

LEE, Taek Jin/B.S.

Staff in charge of writing the report: LEE, Taek Jin/B.S.

Contents

1. Summary

In order to conduct a single oral administration toxicity test of silver ion water generated from a silver ion sterilizer, we orally administered silver ion water of 1000 and 500 mg/kg B.W. one time each to female rates and male rates, respectively, with a common ratio of 2, and a maximum volume of 2000 mg/kg B.W. according to the "Toxicity Test Standards for Drugs etc." of the Ministry of Food & Drug Safety Announcement. We observed the mortality rate, general symptoms and weight changes during 14 days since administration of the test substance, and conducted an autopsy on animals that survived and observed with unaided eyes for any abnormalities in the organs.

-There were no animals that died due to administration of the test substances during the testing period.

-There were no abnormal findings caused by administration of the test substances as a result of observing general symptoms.

-There were no significant statistical difference between the group administered with the test substances and the control group, according to measurements of weights of the animals survived.

-There were no abnormal findings in any of the groups as a result of conducting an autopsy on the animals survived.

Accordingly, since there is no observable toxicity related to the test substances when conducting a single oral administration of silver ion water generated by silver ion sterilizers on rats, approximate lethal doses for female rats and male rats are considered to be more than 2000 mg/kg B.W.

2. Introduction

This study was conducted to evaluate the toxic reactions that would appear after making a single (one time) oral administration of silver ion water generated from a silver ion sterilizer to SD rats.

This study was conducted with the approval from the Animal Ethics Committee of the Health Care Research Laboratory of the Korea Testing & Research Institute (KTR) based on the Animals Protection Act[enforcement Aug. 14 2014][Regulation no. 12051(partially amended on Aug. 13, 2013) and the Regulations on Animals for Testing[Enforcement Jul. 30, 2013][Regulation no. 11987(partially amended on Jul. 30, 2013)].

2.1 Test Schedule

Study initiation date	: September 17, 2014
Test initiation date	: October 16, 2014
Date of animal adoption	: October 16, 2014
Quarantine and Purification period	: October 16, 2014 ~ October 20, 2014
Group separation date	: October 20, 2014
General symptom observation period	: October 21, 2-14 ~ November 4, 2014
Autopsy date	: November 4, 2014
Test end date	: November 4, 2014
Study end date	: November 13, 2014

3. Materials & Methods

3.1 Test substances and diluting agent

3.1.1 Test substances

Name of substance : Silver ion sterilizer

Origin of supply: CNL Co., Ltd.

Date of production: September 1, 2014

Installation date: October 6, 2014

Installed device: Silver ion water producing device set 1

Storing condition during test period: room temperature[(1-30)℃], to be used on the same day it is produced

Appearance and state: Transparent liquid when produced as silver ion water

Effective life period: Until silver plates perish (provided by sponsor)

Disposal of remaining test substance: Discard silver ion water and return producing device set 1

3.2 Fabrication of Test Substances

We diluted the test substances generated from the silver ion water sterilizer with diluting agents of sterilized distilled water(main water used) of concentrations of 50 mg/mL, 100 mg/mL and 200 mg/mL.

3.3 Analyses on Test Substances

We decided not to conduct a separate analysis on the concentration, safety and homogeneity of the test substances and administered liquid after discussing with the test sponsor.

3.4 Test specifications

Type and species: Crl:CD(SD), Rat, SPF

Origin of supply: Orient Bio Co., Ltd. (8 124-bun-gil, HwaAkSan-ro, Bukmyeon, Gapyeong-gun, Gyeonggi-do)

Gender and number of animals when adopted : 21 male, and 21 females

Age and weight of animals when adopted : 5 weeks old, male 141.7g ~ 164.9 g

Female 105.8 g ~ 117.2 g

Gender and number of animals at administration : 20 male, and 20 female

Age and weight of animals at administration : 6 weeks old, male 163.7g ~ 180.g

Female 119.2 g ~ 129.6g

3.4.1 Reason for selecting the test specifications

The SD rats used in this study are rats that are widely being used in safety tests including single administration toxicity tests, and there are abundant basic data accumulated, thereby enabling easy interpretation and evaluation of the results.

3.4.2 Quarantine and purification

We quarantined and purified and observed the general heath conditions of the rats under animal raising environment of the Health Care Research Laboratory of the Korea Testing & Research Institute for 5 days since adoption of the animals, and then selected healthy rats to be used in the test.

3.4.3 Entity identification

We marked the entity numbers on the tail of each rat with a oil-based pen, and attached entity ID cards to the cage.

3.4.4 Grouping

We selected the healthy rats after purification, and grouped the rats randomly such that each group has the same average weight and standard deviation.

3.4.5 Disposal of remaining animals

After the grouping, we euthanized the remaining animals.

3.5 Raising environment

3.5.1 Number of animals rooms

Quarantine and purification : Clean Animal Raising Room 12

Test & Observation: Clean Animal Raising Room 11

3.5.2 Environmental conditions

Temperature: (21.3 ~ 22.5)℃

Relative humidity: (44.1 ~ 56.1) % R.H.

Number of times of ventilation: (10 ~ 20) times/h

Lighting cycle: Bright condition 12 hours (08:00 ~ 20:00)

Dark condition 12 hours (20:00 ~ 08:00)

Illumination: (150 ~ 300) Lux

Cage type: Stainless steel wire cage

Cage size: (310W x 500D x 200H)mm

Capacity per cage: No more than 3 animals

The temperature and humidity of the animal room was measured every 30 minutes by an automatic temperature humidity measuring device, and environmental conditions such as the illumination was measured according to the standard operation guidelines. As a result of measuring the environment of the animal room, there were no factors affecting the test.

3.5.3 Feed and drinking water supply

Radiation sterilized Labdiet 5L79 [Labdiet, USA] was used as the feed, and R/O water was

provided as free drinking water.

3.5.4 Feed and drinking water inspection

We inspected the feed based on the analysis report that had been prepared under regular inspections by the manufacturer of the feed that we received from the feed supplier, and we inspected the drinking water for any effects on the test based on the regular inspections according to the standard operation guidelines of the Health Care Research Laboratory of Korea Testing and Research Institute, but found none.

4. Test method

4.1 Volume setting

The amount of test substances to be administered was set to 2000 mg/kw B.W. for the group with the highest amount of administration based on the "Toxicity Test Standards of Drugs etc.", and then 1000 and 500 mg/kg B.W. for the group with the intermediate amount of administration and the group with low amount of administration, respectively, with a common ratio of 2. The control group was administered with the diluting agent, sterilized distilled water (main water used).

4.2 Group configuration

Test group	Gender	Number of animals	Animal number	Administered amount (mg/kg B.W.)	Administered liquid amount (mL/kg B.W.)	Administration route
G1	Female	5	1101-1105	0	10	Oral administration
	Male	5	2101-2102			
G2	Female	5	1201-1205	500	10	
	Male	5	2201-2205			
G3	Female	5	1301-105	1000	10	
	Male	5	2301-2305			
G4	Female	5	1401-1405	2000	10	
	Male	5	2401-2405			

※ G1: Control group with diluting agent,

G2: Group with low amount of administration

G3: Group with intermediate amount of administration

G4: Group with the highest amount of administration

4.3 Administration route and method of test substances

After putting the animals on an abstemious diet for about 18 hours, we forcibly administered the test substance once to the stomach of each animal using a syringe having a sonde for oral administration.

4.4 Observation items

4.4.1 General symptoms

We observed all the animals once a day, for 14 days since the administration. However, on the day of administration, we observed the animals 0.5, 1, 2, 3, and 4 hours after the administration.

4.4.2 Weight changes

We measured the weights of the animals when adopted, when dividing them into groups, just before administering test substances, 7 days after administration, and on the 14^{th} day of administration.

4.4.3 Autopsy report

We conducted an appearance inspection on all the animals survived on the 14^{th} day of administration, and then conducted an autopsy and examined the organs with unaided eyes.

4.5 Statistical processing

In this test, we conducted a statistical processing on weight data using an SPSS(Ver 19.0) statistics program. First of all, we conducted an equal variance inspection through a Levene's test, and then a one way ANOVA inspection(variance analysis), but no

significance was observed from both male and female rats.

5. Results

5.1 Mortality and general symptoms (Table 1, 2 and Appendix 1, 2)

There was no dead animals or abnormal findings caused by the administration of test substances during the test period.

5.2 Weight changes (Table 3, Appendix 3, 4)

All the animals showed normal increase of weight.

5.3 Autopsy report (Table 4, Appendix 5, 6)

There was no abnormal finding in all the animals caused by the administration of test substances according to observation on the major organs with unaided eyes.

6. Discussion & conclusion

In order to conduct a single oral administration toxicity test of silver ion water generated from a silver ion sterilizer, we orally administered silver ion water of 1000 and 500 mg/kg B.W. one time each to female rates and male rates, respectively, with a common ratio of 2, and a maximum volume of 2000 mg/kg B.W. according to the "Toxicity Test Standards for Drugs etc." of the Ministry of Food & Drug Safety Announcement. We observed the mortality rate, general symptoms and weight changes during 14 days since administration of the test substance, and conducted an autopsy on animals that survived and observed with unaided eyes for any abnormalities in the organs.

-There were no animals that died due to administration of the test substances during the testing period.

-There were no significant statistical difference between the group administered with the test substances and the control group, according to measurements of weights of the animals survived.

-There were no abnormal findings in any of the groups as a result of conducting an autopsy on the animals survived.

Accordingly, since there is no observable toxicity related to the test substances when conducting a single oral administration of silver ion water generated by silver ion sterilizers on rats, approximate lethal doses for female rats and male rats are considered to be more than 2000 mg/kg B.W.

7. References

- Ministry of Food & Drug Safety Announcement no. 2014-67 (Feb. 12, 2014) "Nonclinical Test Management Standards"

- Ministry of Food & Drug Safety Announcement no. 2014-6 (Jan. 29, 2014) [Attachment 1] Single administration toxicity test of "Toxicity Test Standards of Drugs"

-National Toxicity Research Institute of the Ministry of Food & Drug Safety: "Guidelines to Toxicity Test Standards of Drugs etc (Dec., 1999)"

-National Institute of Food & Drug Safety Evaluation of the Ministry of Food & Drug Safety Announcement ""Guidelines to Toxicity Test Standards of Drugs etc. (Dec., 2012)

-OECD Principle of Good Laboratory Practice, ENV/MC/CHEM (98)17 (as revised in 1997)

8. Tables (Group summary)

Table 1. Mortality

Group	Dose (mg/kg B.W.)	Mortality	
		Male	Female
G1	0	0% (0 / 5)[a]	0% (0 / 5)
G2	500	0% (0 / 5)	0% (0 / 5)
G3	1000	0% (0 / 5)	0% (0 / 5)
G4	2000	0% (0 / 5)	0% (0 / 5)

[a] : No. of dead animals / No. of tested animals

Table 2. Clinical signs

Group	Dose (mg/kg B.W.)	Sex	Number of animal	Clinical signs
G1	0	Male	5	N
		Female	5	N
G2	500	Male	5	N
		Female	5	N
G3	1000	Male	5	N
		Female	5	N
G4	2000	Male	5	N
		Female	5	N

N : Normal

Table 3. Body weight

Unit : g

Group	Dose (mg/kg B.W.)	Sex		Days after administration		
				0	7	14
G1	0	Male	Mean	173.9	259.3	314.4
			S.D.	4.0	9.7	17.2
			N	5	5	5
		Female	Mean	125.1	172.5	194.6
			S.D.	3.7	4.1	8.0
			N	5	5	5
G2	500	Male	Mean	173.8	260.0	315.1
			S.D.	6.1	8.3	7.9
			N	5	5	5
		Female	Mean	122.6	173.2	197.5
			S.D.	2.4	9.3	18.0
			N	5	5	5
G3	1000	Male	Mean	169.8	261.3	316.8
			S.D.	7.5	5.2	5.2
			N	5	5	5
		Female	Mean	124.4	177.0	203.3
			S.D.	2.9	9.4	13.1
			N	5	5	5
G4	2000	Male	Mean	170.5	258.3	308.2
			S.D.	4.0	9.3	12.1
			N	5	5	5
		Female	Mean	121.6	172.7	206.7
			S.D.	2.9	15.0	8.9
			N	5	5	5

N : Number of animals, S.D. : Standard deviation

Table 4. Necropsy findings

Findings		Group (mg/kg B.W.)							
		G1 (0)		G2 (500)		G3 (1000)		G4 (2000)	
		Male	Female	Male	Female	Male	Female	Male	Female
Number of animals		5	5	5	5	5	5	5	5
External findings	No gross findings	5	5	5	5	5	5	5	5
Internal findings	No gross findings	5	5	5	5	5	5	5	5

9. Appendices (Individual data)

Appendix 1. Clinical signs of male rats

Group	Dose (mg/kg B.W.)	Animal number	Hours after administration					Days after administration			
			0.5 h	1 h	2 h	3 h	4 h	1	2	3	4
G1	0	1101	N	N	N	N	N	N	N	N	N
		1102	N	N	N	N	N	N	N	N	N
		1103	N	N	N	N	N	N	N	N	N
		1104	N	N	N	N	N	N	N	N	N
		1105	N	N	N	N	N	N	N	N	N
G2	500	1201	N	N	N	N	N	N	N	N	N
		1202	N	N	N	N	N	N	N	N	N
		1203	N	N	N	N	N	N	N	N	N
		1204	N	N	N	N	N	N	N	N	N
		1205	N	N	N	N	N	N	N	N	N
G3	1000	1301	N	N	N	N	N	N	N	N	N
		1302	N	N	N	N	N	N	N	N	N
		1303	N	N	N	N	N	N	N	N	N
		1304	N	N	N	N	N	N	N	N	N
		1305	N	N	N	N	N	N	N	N	N
G4	2000	1401	N	N	N	N	N	N	N	N	N
		1402	N	N	N	N	N	N	N	N	N
		1403	N	N	N	N	N	N	N	N	N
		1404	N	N	N	N	N	N	N	N	N
		1405	N	N	N	N	N	N	N	N	N

N : Normal

Appendix 1. (Continued)

Group	Dose (mg/kg B.W.)	Animal number	Days after administration									
			5	6	7	8	9	10	11	12	13	14
G1	0	1101	N	N	N	N	N	N	N	N	N	N
		1102	N	N	N	N	N	N	N	N	N	N
		1103	N	N	N	N	N	N	N	N	N	N
		1104	N	N	N	N	N	N	N	N	N	N
		1105	N	N	N	N	N	N	N	N	N	N
G2	500	1201	N	N	N	N	N	N	N	N	N	N
		1202	N	N	N	N	N	N	N	N	N	N
		1203	N	N	N	N	N	N	N	N	N	N
		1204	N	N	N	N	N	N	N	N	N	N
		1205	N	N	N	N	N	N	N	N	N	N
G3	1000	1301	N	N	N	N	N	N	N	N	N	N
		1302	N	N	N	N	N	N	N	N	N	N
		1303	N	N	N	N	N	N	N	N	N	N
		1304	N	N	N	N	N	N	N	N	N	N
		1305	N	N	N	N	N	N	N	N	N	N
G4	2000	1401	N	N	N	N	N	N	N	N	N	N
		1402	N	N	N	N	N	N	N	N	N	N
		1403	N	N	N	N	N	N	N	N	N	N
		1404	N	N	N	N	N	N	N	N	N	N
		1405	N	N	N	N	N	N	N	N	N	N

N : Normal

(End)

Appendix 2. Clinical signs of female rats

Group	Dose (mg/kg B.W.)	Animal number	Hours after administration					Days after administration			
			0.5 h	1 h	2 h	3 h	4 h	1	2	3	4
G1	0	2101	N	N	N	N	N	N	N	N	N
		2102	N	N	N	N	N	N	N	N	N
		2103	N	N	N	N	N	N	N	N	N
		2104	N	N	N	N	N	N	N	N	N
		2105	N	N	N	N	N	N	N	N	N
G2	500	2201	N	N	N	N	N	N	N	N	N
		2202	N	N	N	N	N	N	N	N	N
		2203	N	N	N	N	N	N	N	N	N
		2204	N	N	N	N	N	N	N	N	N
		2205	N	N	N	N	N	N	N	N	N
G3	1000	2301	N	N	N	N	N	N	N	N	N
		2302	N	N	N	N	N	N	N	N	N
		2303	N	N	N	N	N	N	N	N	N
		2304	N	N	N	N	N	N	N	N	N
		2305	N	N	N	N	N	N	N	N	N
G4	2000	2401	N	N	N	N	N	N	N	N	N
		2402	N	N	N	N	N	N	N	N	N
		2403	N	N	N	N	N	N	N	N	N
		2404	N	N	N	N	N	N	N	N	N
		2405	N	N	N	N	N	N	N	N	N

N : Normal

Appendix 2. (Continued)

Group	Dose (mg/kg B.W.)	Animal number	Days after administration									
			5	6	7	8	9	10	11	12	13	14
G1	0	2101	N	N	N	N	N	N	N	N	N	N
		2102	N	N	N	N	N	N	N	N	N	N
		2103	N	N	N	N	N	N	N	N	N	N
		2104	N	N	N	N	N	N	N	N	N	N
		2105	N	N	N	N	N	N	N	N	N	N
G2	500	2201	N	N	N	N	N	N	N	N	N	N
		2202	N	N	N	N	N	N	N	N	N	N
		2203	N	N	N	N	N	N	N	N	N	N
		2204	N	N	N	N	N	N	N	N	N	N
		2205	N	N	N	N	N	N	N	N	N	N
G3	1000	2301	N	N	N	N	N	N	N	N	N	N
		2302	N	N	N	N	N	N	N	N	N	N
		2303	N	N	N	N	N	N	N	N	N	N
		2304	N	N	N	N	N	N	N	N	N	N
		2305	N	N	N	N	N	N	N	N	N	N
G4	2000	2401	N	N	N	N	N	N	N	N	N	N
		2402	N	N	N	N	N	N	N	N	N	N
		2403	N	N	N	N	N	N	N	N	N	N
		2404	N	N	N	N	N	N	N	N	N	N
		2405	N	N	N	N	N	N	N	N	N	N

N : Normal

(End)

Appendix 3. Body weight of male rats

Unit : g

Group	Dose (mg/kg B.W.)	No.	Days after administration		
			0	7	14
G1	0	1101	176.5	246.0	292.4
		1102	178.3	270.1	335.9
		1103	172.2	267.4	323.0
		1104	168.0	257.7	318.4
		1105	174.6	255.3	302.3
		Mean	173.9	259.3	314.4
		S.D.	4.0	9.7	17.2
G2	500	1201	180.9	271.9	326.9
		1202	176.9	257.5	315.1
		1203	164.3	249.0	305.1
		1204	173.9	259.8	312.4
		1205	172.9	262.0	316.1
		Mean	173.8	260.0	315.1
		S.D.	6.1	8.3	7.9
G3	1000	1301	163.8	257.6	309.2
		1302	163.7	255.9	319.2
		1303	178.8	269.2	323.1
		1304	165.8	260.7	318.1
		1305	177.0	263.1	314.5
		Mean	169.8	261.3	316.8
		S.D.	7.5	5.2	5.2
G4	2000	1401	165.5	243.8	291.4
		1402	173.4	262.5	307.9
		1403	167.0	254.9	304.3
		1404	172.4	262.8	313.3
		1405	174.2	267.7	324.3
		Mean	170.5	258.3	308.2
		S.D.	4.0	9.3	12.1

S.D. : Standard deviation

Appendix 4. Body weight of female rats

Unit : g

Group	Dose (mg/kg B.W.)	No.	Days after administration		
			0	7	14
G1	0	2101	129.6	176.0	197.5
		2102	122.4	177.1	206.7
		2103	120.6	169.9	191.6
		2104	127.8	172.5	185.4
		2105	125.3	167.2	191.8
		Mean	125.1	172.5	194.6
		S.D.	3.7	4.1	8.0
G2	500	2201	120.5	161.7	170.7
		2202	126.5	166.4	192.3
		2203	123.0	183.6	219.3
		2204	122.0	173.2	199.4
		2205	120.8	180.9	205.8
		Mean	122.6	173.2	197.5
		S.D.	2.4	9.3	18.0
G3	1000	2301	121.4	177.0	202.0
		2302	126.9	185.9	211.7
		2303	127.6	185.9	214.1
		2304	121.4	172.4	207.5
		2305	124.5	163.7	181.4
		Mean	124.4	177.0	203.3
		S.D.	2.9	9.4	13.1
G4	2000	2401	120.1	175.1	203.2
		2402	121.5	186.0	219.1
		2403	120.4	168.5	203.1
		2404	119.2	149.2	196.2
		2405	126.6	184.8	211.8
		Mean	121.6	172.7	206.7
		S.D.	2.9	15.0	8.9

S.D. : Standard deviation

Appendix 5. Necropsy findings of male rats

Animal No.	1101	Group : G1 Dose :	0	mg/kg	Terminal sacrifice	: Day 14
External findings : No gross findings Internal findings : No gross findings						
Animal No.	1102	Group : G1 Dose :	0	mg/kg	Terminal sacrifice	: Day 14
External findings : No gross findings Internal findings : No gross findings						
Animal No.	1103	Group : G1 Dose :	0	mg/kg	Terminal sacrifice	: Day 14
External findings : No gross findings Internal findings : No gross findings						
Animal No.	1104	Group : G1 Dose :	0	mg/kg	Terminal sacrifice	: Day 14
External findings : No gross findings Internal findings : No gross findings						
Animal No.	1105	Group : G1 Dose :	0	mg/kg	Terminal sacrifice	: Day 14
External findings : No gross findings Internal findings : No gross findings						
Animal No.	1201	Group : G2 Dose :	500	mg/kg	Terminal sacrifice	: Day 14
External findings : No gross findings Internal findings : No gross findings						
Animal No.	1202	Group : G2 Dose :	500	mg/kg	Terminal sacrifice	: Day 14
External findings : No gross findings Internal findings : No gross findings						
Animal No.	1203	Group : G2 Dose :	500	mg/kg	Terminal sacrifice	: Day 14
External findings : No gross findings Internal findings : No gross findings						
Animal No.	1204	Group : G2 Dose :	500	mg/kg	Terminal sacrifice	: Day 14
External findings : No gross findings Internal findings : No gross findings						
Animal No.	1205	Group : G2 Dose :	500	mg/kg	Terminal sacrifice	: Day 14
External findings : No gross findings Internal findings : No gross findings						

Appendix 5. (Continued)

Animal No.	1301	Group : G3	Dose :	1000	mg/kg	Terminal sacrifice	: Day 14
External findings : No gross findings Internal findings : No gross findings								
Animal No.	1302	Group : G3	Dose :	1000	mg/kg	Terminal sacrifice	: Day 14
External findings : No gross findings Internal findings : No gross findings								
Animal No.	1303	Group : G3	Dose :	1000	mg/kg	Terminal sacrifice	: Day 14
External findings : No gross findings Internal findings : No gross findings								
Animal No.	1304	Group : G3	Dose :	1000	mg/kg	Terminal sacrifice	: Day 14
External findings : No gross findings Internal findings : No gross findings								
Animal No.	1305	Group : G3	Dose :	1000	mg/kg	Terminal sacrifice	: Day 14
External findings : No gross findings Internal findings : No gross findings								
Animal No.	1401	Group : G4	Dose :	2000	mg/kg	Terminal sacrifice	: Day 14
External findings : No gross findings Internal findings : No gross findings								
Animal No.	1402	Group : G4	Dose :	2000	mg/kg	Terminal sacrifice	: Day 14
External findings : No gross findings Internal findings : No gross findings								
Animal No.	1403	Group : G4	Dose :	2000	mg/kg	Terminal sacrifice	: Day 14
External findings : No gross findings Internal findings : No gross findings								
Animal No.	1404	Group : G4	Dose :	2000	mg/kg	Terminal sacrifice	: Day 14
External findings : No gross findings Internal findings : No gross findings								
Animal No.	1405	Group : G4	Dose :	2000	mg/kg	Terminal sacrifice	: Day 14
External findings : No gross findings Internal findings : No gross findings								

(End)

Appendix 6. Necropsy findings of female rats

Animal No.	2101	Group : G1 Dose :	0	mg/kg	Terminal sacrifice	: Day 14
External findings : No gross findings Internal findings : No gross findings							
Animal No.	2102	Group : G1 Dose :	0	mg/kg	Terminal sacrifice	: Day 14
External findings : No gross findings Internal findings : No gross findings							
Animal No.	2103	Group : G1 Dose :	0	mg/kg	Terminal sacrifice	: Day 14
External findings : No gross findings Internal findings : No gross findings							
Animal No.	2104	Group : G1 Dose :	0	mg/kg	Terminal sacrifice	: Day 14
External findings : No gross findings Internal findings : No gross findings							
Animal No.	2105	Group : G1 Dose :	0	mg/kg	Terminal sacrifice	: Day 14
External findings : No gross findings Internal findings : No gross findings							
Animal No.	2201	Group : G2 Dose :	500	mg/kg	Terminal sacrifice	: Day 14
External findings : No gross findings Internal findings : No gross findings							
Animal No.	2202	Group : G2 Dose :	500	mg/kg	Terminal sacrifice	: Day 14
External findings : No gross findings Internal findings : No gross findings							
Animal No.	2203	Group : G2 Dose :	500	mg/kg	Terminal sacrifice	: Day 14
External findings : No gross findings Internal findings : No gross findings							
Animal No.	2204	Group : G2 Dose :	500	mg/kg	Terminal sacrifice	: Day 14
External findings : No gross findings Internal findings : No gross findings							
Animal No.	2205	Group : G2 Dose :	500	mg/kg	Terminal sacrifice	: Day 14
External findings : No gross findings Internal findings : No gross findings							

Appendix 6. (Continued)

Animal No.	2301	Group : G3	Dose :	1000	mg/kg	Terminal sacrifice	: Day 14
External findings : No gross findings Internal findings : No gross findings								
Animal No.	2302	Group : G3	Dose :	1000	mg/kg	Terminal sacrifice	: Day 14
External findings : No gross findings Internal findings : No gross findings								
Animal No.	2303	Group : G3	Dose :	1000	mg/kg	Terminal sacrifice	: Day 14
External findings : No gross findings Internal findings : No gross findings								
Animal No.	2304	Group : G3	Dose :	1000	mg/kg	Terminal sacrifice	: Day 14
External findings : No gross findings Internal findings : No gross findings								
Animal No.	2305	Group : G3	Dose :	1000	mg/kg	Terminal sacrifice	: Day 14
External findings : No gross findings Internal findings : No gross findings								
Animal No.	2401	Group : G4	Dose :	2000	mg/kg	Terminal sacrifice	: Day 14
External findings : No gross findings Internal findings : No gross findings								
Animal No.	2402	Group : G4	Dose :	2000	mg/kg	Terminal sacrifice	: Day 14
External findings : No gross findings Internal findings : No gross findings								
Animal No.	2403	Group : G4	Dose :	2000	mg/kg	Terminal sacrifice	: Day 14
External findings : No gross findings Internal findings : No gross findings								
Animal No.	2404	Group : G4	Dose :	2000	mg/kg	Terminal sacrifice	: Day 14
External findings : No gross findings Internal findings : No gross findings								
Animal No.	2405	Group : G4	Dose :	2000	mg/kg	Terminal sacrifice	: Day 14
External findings : No gross findings Internal findings : No gross findings								

(End)

10. Figure

Figure 1. Test substance